comprising a therapeutically effective amount of a neuroactive agent other than the Slit-N polypeptide.

24. (New) A pharmaceutical composition comprising a therapeutically effective amount of a Slit-N polypeptide according to claim 19, and a pharmaceutically acceptable excipient, further comprising a therapeutically effective amount of a neuroactive agent other than the Slit-N polypeptide, wherein the agent is NGF.

A3 cont'd

25. (New) A method of promoting axon branching or sprouting, comprising contacting a neuron with a composition comprising an effective amount of a Slit-N polypeptide according to claim 19.

26. (New) A method of treating a neuropathy comprising administering a composition comprising a therapeutically effective amount of a Slit-N polypeptide according to claim 19.

REMARKS

Amendments

The specification is amended to correct a minor typo; claim 1 is amended to clarify the Slit-N polypeptide (support for natural sequence Slit-N polypeptides is found, inter alia, on p.3, lines 14, 24, 25, 27, p.4, line 1); claim 2 is amended to employ markush language and claims 2 and 7 are amended to provide terminal punctuation. These amendments introduce no new matter.

Restriction

We confirm election of group I and upon allowance of the product claims of group I, seek rejoinder of the duly limited method claims of groups III and IV.

35USC119(e)

Applicants have re-requested insertion of a specific reference (by serial number) of the prior application (see also our preliminary amendment mailed July 9, 1999).

Double Patenting

The claimed invention is patentably distinct from that claimed in Goodman et al. (US Patent No.6,046,015). The cited patent describes and claims slit fragments generally, but there is no mention of, no suggestion of, nor claims to natural sequence Slit-N polypeptides as claimed herein.

Note that prior to the present disclosure, the art taught that Slit proteins were chemorepellents (for background, see Brose et al. (1999) and Wu et al. (1999), both attached). There is no prior art suggestion of the surprising finding, disclosed herein, that these polypeptides "function as positive regulators of axon collateral formation during the establishment or remodeling of neural circuits and that the activity of these proteins can synergize in vitro and in vivo with other neurotrophic agents like NGF ... that Slit-N proteins can function to regulate axon collateralization not just during the initial development of axonal connections, but also during normal plastic rearrangements of neural connections that occur in the adult nervous system ... [and that] following injury to the spinal cord, Slit-N proteins can induce regeneration by stimulating collateralization of axons from fiber tracts into the CNS gray matter, and/or axon regrowth in an inhibitory environment, to help alleviate the paralysis that accompanies injury to fiber tracts. Specification at p.1., line 25 - p.2, line 4.

For good measure, Applicants provide an expert Declaration confirming that the claimed subject matter of Goodman et al. and that presently claimed are patentably distinct.

35USC112, first paragraph

Slit-N polypeptides, and particularly natural sequence Slit-N polypeptides, are consistently defined. Natural sequence Slit-N polypeptides are known in the art to refer to a class of proteins naturally produced as N-terminal proteolytic fragments of Slit polypeptides. Natural sequence Slit-N polypeptides are naturally occurring N-terminal proteolytic fragments of Slit proteins which stimulate elongation and branching of neuronal axons. Residue boundaries of natural sequence Slit-N polypeptides are readily determined (see, p.6, lines 2-29) and exemplified, e.g. hSlit-2-N is bound by Met1 and Arg1117 of hSlit-2; dSlit-2-N is bound by Met1 and Gln1111 of dSlit (see, p.3, lines 26-27).

Furthermore, Slit proteins are an art recognized class of neuroactive proteins and diverse and numerous examples of Slit proteins were known as of March 19, 1999. For example, Brose et al. (1999) describes human (h) Slit polypeptides: hSlit-1, hSlit-2, hSlit-3; rat (r) Slit polypeptides: rSlit-1, rSlit-2, rSlit-3; as well as Slit polypeptides from Drosophila and C. elegans. See Brose at p.796. Applicants need not burden their disclosure with sequence recitations of well known proteins.

Slit-N polypeptides are structurally and functionally described: arbitrary internal Slit fragments and full length Slit proteins are clearly not encompassed by natural sequence Slit-N polypeptides and the activity of Slit-N polypeptides is distinct from the chemorepellant activity associated with Slit proteins (see also, p.8, line 8).

Applicants' claims clearly contrast with those of *Ex parte Maizel*, 27 USPQ2d 1662 (BPAI 1992) which not only encompassed nucleic acids encoding Maizel's disclosed protein but went on to include any "biological functional equivalent thereof" or a protein which "corresponds biologically to."

For good measure, Applicants provide an expert Declaration confirming that the disclosure clearly conveys to those skilled in the art the Applicants had possession of the invention and enables those of ordinary skill in the art to practice the invention without undue experimentation.

35USC112, second paragraph

Claims 2 and 7 have been amended to provide terminal punctuation.

Claim 3 is believed to be clear in further limiting the polypeptide of claim 1 to be contained in a pharmaceutical composition. Such compositions are thoroughly described and exemplified, e.g. p.6, line 20 - p.7, line 26.

Claims 6-9 are believed to be clear in reciting a therapeutically effective amount (in reference to the recited Slit-N polypeptide and the recited neuroactive agent). Such amounts are described and exemplified on p.6, lines 16 - p.7, line 26; p.8, lines 21-25; p.11, lines 10-14. The desired therapeutic effect is to promote nerve regeneration and treat neuropathy, which is the subject of this invention; see, e.g. title; field of the invention; p.1, line 25 - p.2, line 4; p.2, line 27 - p.3, line 3, etc.

35USC102(e)

The cited Artavanis-Tsakonas patent describes a human Notch protein. Like human Slit proteins, human notch is well-known. Human notch is known to be structurally and functionally unrelated to Slit and Slit-N polypeptides. Not only is this fact well known in the art but it is readily confirmed by simply comparing the known disparate sequences of these proteins (Brose et al. vs. Artavanis-Tsakonas et al.).

Goodman et al. (US Patent No.6,046,015) describes and claims slit fragments generally, but there is no mention or suggestion of natural sequence Slit-N polypeptides.

For good measure, Applicants provide an expert Declaration confirming that the cited art does not teach or suggest the claimed natural sequence Slit-N polypeptides or methods of use. Absent a prior art disclosure teaching or suggesting the subject natural sequence Slit-N polypeptides, the claims are in compliance with 35USC102 and 103.

The Examiner is invited to call the undersigned if he would like to amend the claims to clarify the foregoing or seeks further clarification of the claim language.

Applicants hereby petition for any necessary extension of time pursuant to 37 CFR 1.136(a). The Commissioner is hereby authorized to charge any fees or credit any overcharges relating to this communication to our Deposit Account No. 19-0750 (order no. UC99-244-2).

Respectfully submitted,
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encl. Brose et al.(12p)
Wu et al.(6p)
132 Declaration (2p)